HFI-35 d1925t
(Betty Dorsey)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

CBER-98-019

JUN 18 1998

WARNING LETTER

CERTIFIED - RETURN RECEIPT REQUESTED

David E. Hatcher
Chairman, President, and CEO
Gamma Biologicals, Incorporated
3700 Mangum Road
Houston, Texas 77092-5497

Dear Mr. Hatcher:

The Food and Drug Administration (FDA) conducted an inspection of Gamma Biologicals, Incorporated, 3700 Mangum Road, Houston, Texas, from April 14, 1998, to April 30, 1998. During the inspection, our FDA investigators documented significant deviations from the applicable standards and requirements of Subchapter F, Parts 600-680, and Subchapter H, Part 820, Title 21, Code of Federal Regulations as follows:

1. Failure to adequately develop, conduct, control, and monitor product processes to ensure that a device conforms to its specifications and that your Blood Grouping Reagent and Anti-Human Globulin products are prepared by a method demonstrated to yield consistently a sterile product, 21 CFR 820.70, 660.20(a), and 660.50(a). For example:

   a. microbial monitoring of the water system was not performed between March 30, 1991, and March 2, 1998;

   b. installation, operation, and performance qualification of the current water system has not been performed;

   c. media fill qualifications of the vialing process have not been performed since 1991;

   d. microbiological challenges have not been performed for the sterilizing filters under conditions reflecting production;

e. the standard operating procedure (SOP) for sterile filtration does not specify the appropriate filter size and type for the filtration of bulk solutions of Anti-Human Globulin and Blood Grouping Reagents, and does not require integrity testing of the filters;

f. the laminar air flow (LAF) hoods used in the Monoclonal Laboratories and the Filtration Room, considered to be certified as Class 100,

(i) are not monitored for non-viable particulates; and

(ii) viable particulate monitoring is not performed for the LAF units in the Filtration Room;

g. installation, operation, and performance qualification has not been performed for [redacted] of the bioreactors used in the production of monoclonal antibodies for Anti-Human Globulin reagents;

h. concerning the validation of Autoclave 2 and Heat Oven A:

(i) installation and operation qualification has not been performed;

(ii) heat distribution studies were not performed for a full chamber load; and

(iii) no protocol and acceptance criteria exists for the heat penetration studies;

i. cleaning validation has not been performed for multi-use equipment used in the Monoclonal Laboratories;

j. microbial monitoring of production personnel in the Monoclonal Laboratories and Vialing Room A is not performed;

k. environmental monitoring is not performed in Monoclonal Laboratory 1, the Filtration Room, and the anteroom of Vialing Room A;

l. pressure differential is not monitored in Monoclonal Lab 2;

m. concerning the [redacted] oftware, used for the handling, storage, and distribution of product:

(i) there is no documentation of validation of the system; and

(ii) there are no SOPs for the use and maintenance of the system; and

n. no SOP exists for cleaning of floors, plastic curtains, ceilings, and walls in Vialing Room A.

2. Failure to establish and maintain adequate procedures to prevent microbiological contamination that can cause hemolysis of your Reagent Red Blood Cell products and failure to ensure that the processing method consistently yields a product that is capable of detecting alloantibodies throughout the dating period, 21 CFR 820.70(e) and 660.34(a). For example, in excess of 366 complaints regarding the inability to use Reagent Red Blood Cell products due to hemolysis or discoloration prior to expiration were reported from September 1997 through March 1998.

3. Failure to establish and maintain procedures for implementing corrective and preventative actions, 21 CFR 820.100, in that:

a. inadequate documentation is available to determine corrections implemented as a result of over three hundred complaints of hemolysis or discoloration prior to expiration in your Reagent Red Blood Cell products;

b. investigations of hemolysis in Reagent Red Blood Cells, presumed to be the result of microbiological contamination, do not include identification of the microbial contaminants;

c. microbial monitoring excursions in Vialing Room A, used to fill and label products, were not investigated nor are microbial isolates identified; and

d. there is no written procedure for trending of microbiological monitoring excursions found in Vialing Room A and the Monoclonal Laboratories.

4. Failure to establish and maintain procedures to control product that does not conform to specified requirements, 21 CFR 820.90, in that:

a. the hemolysis of lot 1202/Reverse Grouping Cells and lot 1202/Coombs Control Cells is attributed to Pseudomonas contamination, however, documentation is not available to support the conclusion; and

b. the hemolysis of lot 0212/Reverse Grouping Cells is attributed to fungal contamination, however, documentation of testing to detect fungal contamination is not available.

5. Failure to adequately control labeling and packaging operations to prevent labeling mixups, 21 CFR 820.120(d), in that:

a. there is no written procedure for reconciliation of vendor purchased labels; and

b. there is no written procedure describing your firm's practice of relabeling or [redacted]product.

6. Failure to validate with a high degree of assurance and approved by established procedures processes that cannot be fully verified by inspection and test, 21 CFR 820.75, in that the inclusion of reprocessed and reclaimed materials in final products has not been validated. In addition, limits have not been established for the number of times a product can be reprocessed and the number of times an expiration date may be extended.

7. Failure to establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements, 21 CFR 820.50, in that:

a. no growth promotion or other periodic verification of the Certificate of Analysis is performed for media used for environmental monitoring and water system microbial testing; and

b. there is no written, approved procedure for purchasing controls.

8. Failure to report important proposed changes in equipment, 21 CFR 601.12, in that the current [redacted]system was not submitted to FDA's Center for Biologics Evaluation and Research (CBER) as a supplement to your establishment license.

9. Failure to identify by suitable means the acceptance status of product, 21 CFR 820.86, in that the investigators observed sterile medium used in the production of monoclonal antibodies in storage without release or quarantine labels.

We acknowledge receipt of your written response dated May 22, 1998, and signed by Mr. John Case and Ms. Susan Batcha, which responded to the inspectional observations. We have reviewed your response, and find that it is inadequate to address our concerns. In general, while your response provides a basic commitment to correct some of the deviations, we are concerned by the lack of specific time frames in which corrections will be effected. In addition, the

response did not provide sufficient documentation to demonstrate that corrections noted as complete have been performed. Moreover, your response does not state whether personnel will be appropriately retrained on revised procedures and processes.

We also have the following specific comments on your response, which are numbered to correspond to the observations listed on the Form FDA 483:

1,2, 3,4 Your response does not address the corrective actions your firm will perform to assure that future corrective and preventative action and nonconforming product investigations are adequate and fully documented.

5a Your response states, and we agree, that 21 CFR does not require Reagent Red Blood Cells to be sterile. Nonetheless, your firm was receiving reports that products were failing to perform throughout the dating period due to microbiologically related hemolysis. This represents a quality issue in your product that should be evaluated, and corrective actions identified and implemented, as part of your corrective and preventative action system.

10 We consider the use of a new or different water system to represent an important change in manufacturing methods that should be submitted as a supplement to your license.

13a Although your response states that you flush the noncirculating ambient temporary water system prior to use, it is unclear whether you have demonstrated that such a procedure will adequately control the system, including the potential build up of biofilm in the [redacted] piping.

13b Your response states that you considered the SOP for the previous water system suitable for the temporary water system, however, the procedure did not adequately designate the temporary system's water outlet ports with the correct numbers. In several instances, some ports were disconnected and no longer in use and existing ports were given a different outlet port number.

14a We recommend that the SOP for [redacted] reference the SOP used for investigations and corrective actions to provide clarity.

14c While we recognize that the reporting form for the [redacted] of the water system indicates that the testing is performed [redacted] the language in the SOP is not as clear. We recommend that you consider modifying the language in the SOP to clearly reflect the frequency.

14d, 16 Your response states that you are considering what useful information could be provided by identifying microbial isolates. We believe that such information is an important component of an adequate investigation. Without such information, we question whether you could appropriately identify and implement needed corrective actions.

15 Your response indicates that the only environmental monitoring microbial excursion in Monoclonal Laboratory #2 occurred on January 20, 1998, and that monitoring repeated on January 23 and 26, 1998, was within specification. However, our review of the documentation collected during the inspection finds that the results of the monitoring on January 26, 1998, were out of specification as well.

18 We believe that monitoring of personnel in the manufacturing environment is a necessary component of a system designed to consistently yield a sterile product in accordance with 21 CFR 660.20 and 660.50.

20a Your response does not address our concern, in that the [redacted]est mentioned is used to determine the integrity of the HEPA filter(s) in the LAF units. The FDA Form 483 observation refers to non-viable particle monitoring in the LAF units which is needed in order for the LAF units to be certified as Class 100.

20c Your response states that you could find only one example of LAF hoods that had not been certified at the specifie[redacted]nterval, however, based on the records of certification provided to the investigators during the inspection, we believe that is incorrect. For example, our review of the records indicate that there was no documentation provided of the appropriate periodic certification of the following LAF hoods: 1) Monoclonal Laboratory #2 LAF hood, no record of certification in early 1997; and 2) Filtration Room LAF hood and LAF panel, no certifications since September 1997 and no certification between January 1997 and September 1997.

21b Your response does not address why the certifications were not performed consistently, for example, some of the certification reports indicate the room was evaluated when not in operation, while others indicate evaluation during operations.

22 Your response does not address whether you will perform non-viable particle monitoring in the identified rooms in order to appropriately classify the rooms.

27b Your response does not state how you will address cleaning of the wood type material in the interim period prior to use of the new vialing room.

28a,b While these observations concerning microbiological challenge of sterilization filters under conditions of use at your facility are similar, we are confused by your response. While you commit to microbial challenges as part of your master validation plan in response to item

28a, you then argue the need to perform such studies in response to item 28b. In addition, while you state that your filter vendors provide you with a Certificate of Analysis for the filters, you should not rely solely on their testing for use of an important component of your firm's ability to perform manufacturing operations that consistently yield a sterile product in accordance with 21 CFR 660.20 and 660.50.

28c,d We disagree with your decision to not institute media fill evaluations of your manufacturing processes for products expected to be sterile. Media fills are a necessary practice used and accepted to validate filling operations that are required to produce product that meets established sterility attributes. If performed correctly, media fills will not contaminate filling equipment.

28e,g We recommend that you reconsider the need for bioburden testing. We believe that it provides valuable information for manufacturing processes intended to consistently yield a sterile product.

30a, b,c Your response did not address item 30c. We do not believe that your reprocessing procedures adequately describe in sufficient detail the criteria and limits (i.e., the reprocessing of lots containing already reprocessed material, repeated extension of expiration dates) to be used in the process. Nor have you described how you intend to validate the process. We believe that you need to revise your SOP to provide criteria and limits for the practice, and validation studies need to be performed. In addition, such procedures, after appropriate validation, should be submitted to CBER for review and approval as a supplement to your product license.

34c2 As an attachment to your response, you include the results printout of the empty chamber heat distribution study in the effort to demonstrate that the chamber drain line was included in the study. Our review notes that the test protocol designated thermocouple [redacted] for the chamber drain line, however, the result print out provided only designates that [redacted] thermocouples were used, and that the thermocouple now representing the drain line has been changed to number [redacted]. The summary report does not indicate that the chamber drain line thermocouple was changed.

35b, 35d2 Your response states that you attribute the failure of two of [redacted] biological indicators in the performance qualification study for Heat Cycle A to your culturing technique, however, there is no documentation to support this view. In addition, your response does not address measures to correct problems you believe that have been identified in your technique.

39 We believe that in accordance with 21 CFR 820.50, you must perform some level of analysis of the media used for environmental monitoring and water testing. We believe that a portion of this analysis would include periodic growth promotion testing of the media.

40,42 Your response states that the [redacted] software will be validated. Please note that the establishment of an adequate validation protocol, including system specifications and criteria for demonstrating that the software will meet the requirements, is necessary in order to conduct adequate validation.

56b,c Your response does not indicate whether facilities or procedures will need to be revised to prevent future issues with adequate segregation of released and quarantined materials or storage of materials in appropriate areas.

Neither the above violations or the observations noted on the Form FDA 483 presented to your firm at the conclusion of the inspection are not intended to be an all-inclusive list of deficiencies at your establishment. It is your responsibility to ensure adherence to each requirement of the Federal Food, Drug, and Cosmetic Act and the applicable regulations and standards. The specific violations noted in this letter and the Form FDA 483 may be symptomatic of serious underlying problems in your establishment's manufacturing and quality systems. You are responsible for investigating and determining the causes of the violations identified by FDA. If the causes are determined to be systems problems you must promptly initiate permanent corrective actions.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action includes license suspension, revocation, and/or denial, seizure and/or injunction, and/or civil penalties. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts. In addition, no license applications or supplements for devices to which the deficiencies are reasonably related will be approved until the violations have been corrected. Moreover, no requests for Certificates to Foreign Governments will be approved until the violations related to the subject devices have been corrected.

You should notify FDA in writing, within 15 working days of receipt of this letter, of specific steps you have taken to correct the noted violations and to prevent their recurrence. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to Mr. Steven A. Masiello, Acting Director, Office of Compliance and Biologics Quality, Food and Drug Administration, Center for Biologics Evaluation and Research, Suite 200N, 1401 Rockville Pike, Rockville, Maryland 20852-1448, ATTN: Division of Case Management, HFM-610.

Sincerely,

Gerald E. Vince
Director, Office of Regional Operations